DK-219-US-X-PCT

DOCKET NO: 259979US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
HIROAKI MATSUNO, ET AL.	: EXAMINER: HAGHIGHTIAN, MINA
SERIAL NO: 10/509,323	:
FILED: MAY 31, 2005	: GROUP ART UNIT: 1616
FOR: THERAPEUTIC COMPOSITION FOR BONE INFECTIOUS DISEASE	:

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

I Masamichi Hashimoto state that:

1. I am a graduate of Waseda University Graduate School and received my master's degree in biochemistry in the year 1984.

2. I have been employed by Denki Kagaku Kogyo Kabushiki Kaisha for 25 years as a researcher.

3. The autocross-linked hyaluronic acid of Example 1 of Bellini (U.S. 6,21,876) is prepared in a similar manner as the cross-linked hyaluronic acid of Example 1 of U.S. Patent 5,676,964, both assigned to Fidia, S.p.A. Therefore, the autocross-linked hyaluronic acid of Bellini are expected to have the same structure as the cross-linked hyaluronic acid of Example 1 of U.S. Patent 5,676,964.

4. The hyaluronic acid gel is a crosslinked hyaluronic acid having a three-dimensional network structure prepared in the manner defined in the above-identified patent application specification at page 21, Example 1.

5. Because the hyaluronic acid gel of the present invention contains very few crosslinks, the difference between the hyaluronic acid used as the starting material and the hyaluronic acid gel could not be detected directly by NMR, IR spectrometry or chemical analysis (quantitative determination of the ester groups according to the saponification method mentioned in column 17, lines 42-44 of U.S. Patent 5,676,964).

6. However, when the crosslinks were concentrated it was found that the crosslinks were ester bonds between carboxyl groups and primary hydroxyl groups in the starting hyaluronic acid and that about 0.1% of the carboxyl groups in the starting hyaluronic acid had formed ester bonds with hydroxyl groups.

7. Concentration procedure: The hyaluornic acid gel of the present invention, prepared in the manner as set forth in Example 1 of the specification, was hydrolyzed with hyaluronidase under such conditions that (uncrosslinked) hyaluronic acid would be hydrolyzed into tetrasaccharides to hexasaccharides and fractionated. As a result, a fraction containing decasaccharides or greater saccharides was obtained, and the decasaccharides and greater saccharides accounted for several percent of the hydrolyzate. The fraction containing decasaccharides or greater saccharides was purified and analyzed by NMR to determine the structure of crosslinks.

8. The cross-linked hyaluronic acid of U.S. Patent 5,676,964 and Bellini (due to the fact that both are made in a similar manner) has both ester bonds and lactonic bonds formed between carboxyl groups and hydroxyl groups.

9. The hyaluronic acid gel of the present invention, prepared in the manner as set forth in Example 1 of the specification, differs from the cross-linked hyaluronic acid of U.S. Patent 5,676,964 and Bellini in that:

A) the hyaluronic acid gel of the present invention does not have lactonic bonds whereas Bellini's has lactonic bonds; and

B) the degree of esterification of the Applicants' hyaluronic acid gel is about 0.1%, whereas the degree of esterification of the cross-linked hyaluronic acid of U.S. Patent 5,676,964 and Bellini is from 1 to 60%, preferably 5 to 30% (column 2, lines 36-41 of U.S. 5,676,964).

10. The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Masamichi Hashimoto

Signature Masamichi Hashimoto

December 10, 2009.

Date

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